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**The Optimal Anti-Coagulation for Enhanced Risk Patients Post-Catheter Ablation for
Atrial Fibrillation (OCEAN) trial**

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Abstract

Background: The optimal long-term antithrombotic regimen for patients after successful catheter-based atrial fibrillation (AF) ablation is not well-defined. Presently, practice variation exists and the benefits of oral anticoagulation (OAC) over antiplatelet therapy across the entire spectrum of stroke risk profile remain undefined in the post-ablation population. To date, there are no randomized trials to inform clinicians on this therapeutic question.

Objective: To assess whether rivaroxaban is superior to acetylsalicylic acid (ASA) in reducing the risk of clinically overt stroke, systemic embolism, or covert stroke among patients without apparent recurrent atrial arrhythmias for at least one year after their most recent AF ablation procedure.

Methods/Design: A prospective, multicenter, open-label, randomized trial with blinded assessment of outcomes is underway (NCT02168829). Atrial fibrillation patients with at least 1 stroke risk factor (as defined by the CHA₂DS₂-VASc score) and without known atrial arrhythmia recurrences for at least 12 months after ablation are randomized to rivaroxaban 15 mg or ASA 75-160 mg daily. The primary outcome is a composite of clinically overt stroke, systemic embolism, and covert stroke based on brain magnetic resonance imaging (MRI). Key secondary outcomes include: major bleeding outcomes, intracranial hemorrhage, transient ischemic attack, neuropsychological testing, quality of life, and an economic analysis. Subjects will be followed for 3 years. The estimated overall sample size is 1572 subjects (786 per arm).

Discussion: The OCEAN trial is a multicenter randomized controlled trial evaluating two antithrombotic treatment strategies for patients with risk factors for stroke after apparently successful AF ablation. We hypothesize that rivaroxaban will reduce the occurrence of clinically overt stroke, systemic embolism, and covert stroke when compared to ASA alone.

Background

Catheter-based atrial fibrillation (AF) ablation is a useful and effective rhythm-control therapy for patients with symptomatic AF. Multiple randomized trials have demonstrated that ablation is superior to anti-arrhythmic drugs in reducing AF recurrence and improving quality of life, particularly for those in whom drugs are ineffective.¹⁻⁴ Accordingly, ablation is an important therapy for patients with symptomatic AF, as reflected in current guidelines and by the considerable rise in procedural volumes over the past decade.^{2,6,7}

The impact of AF ablation on stroke prevention is not well-defined. Ongoing trials which address the prognostic impact of rhythm-control therapies including AF ablation, such as the Early Treatment of Atrial Fibrillation for Stroke Prevention trial (EAST; NCT01288352), Catheter Ablation vs. Anti-arrhythmic Drug Therapy for Atrial Fibrillation trial (CABANA; NCT00911508), and Rhythm Control - Catheter Ablation With or Without Anti-arrhythmic Drug Control of Maintaining Sinus Rhythm Versus Rate Control With Medical Therapy and/or Atrio-ventricular Junction Ablation and Pacemaker Treatment for Atrial Fibrillation (RAFT-AF; NCT01420393) will provide insight on this question. Yet, it is not uncommon for clinicians and/or patients to consider discontinuation of oral anticoagulation (OAC) after ablation. For many patients, the desire to stop anticoagulation is a prime motivation for ablation. Current guidelines, however, recommend continuation of OAC based on clinical risk scoring, irrespective of procedural outcome.^{2,3} Observational studies suggested that the risk of stroke or transient ischemic attack (TIA) among patients who discontinued OAC after "successful" AF ablation could be as low as 0.7% per year.⁹⁻¹⁸ Although this seems to support the notion that the embolic risk of AF patients with successful ablation may be low enough to justify discontinuation of OAC, these studies are limited by short follow-up periods and their

retrospective, non-randomized design which make them susceptible to confounding.⁹⁻¹⁸ As well, these studies had low event rates since they primarily included patients with few medical co-morbidities.⁹⁻¹⁸ Presently, there are no randomized trials to inform clinicians on whether successful AF ablation sufficiently reduces patients' risk of stroke to a point where long-term use of OAC is obviated, particularly at a time when non-vitamin K oral anticoagulants (NOAC) are widely used in clinical practice.

Current AF guidelines generally support continuation of OAC after apparently successful catheter ablation, but they reflect the paucity of high-quality data to inform practice. The Canadian guidelines recommend that OAC should be discontinued after ablation if the patient's long-term risk of stroke is low and in the presence of sustained normal sinus rhythm.² Recognizing the absence of randomized controlled data on this topic, European AF guidelines recommend that the decision to continue with OAC should follow general anticoagulation recommendations regardless of rhythm status.³ Similarly, the 2017 Heart Rhythm Society/European Heart Rhythm Society/ European Cardiac Arrhythmia Society/Asia Pacific Heart Rhythm Society/Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (HRS/EHRA/ECAS/APHRS/SOLAECE) expert consensus statement on catheter and surgical ablation of AF stated that the decision to continue with OAC at more than 2 months post-ablation should be based on the patient's stroke risk profile as opposed to the perceived success or failure of the procedure.⁴ Finally, performing catheter ablation to restore sinus rhythm for the "sole intent of obviating the need for anticoagulation" is a class III recommendation (level of evidence: C) in the 2014 American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS) guidelines.⁵ The cautious wording of these recommendations underscores the lack of data to inform clinicians on the optimal long-term

antithrombotic management for patients after AF ablation. In fact, the new 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of AF lists the management of OAC post-AF ablation as the number one unknown question in our field.⁴ In the 2016 European Society of Cardiology AF guidelines and the Venice Chart international consensus statement on AF ablation, the optimal long-term management of OAC after ablation is a "key unresolved question".^{3,19}

The Optimal Anti-Coagulation for Enhanced Risk Patients Post-Catheter Ablation for Atrial Fibrillation trial (OCEAN trial; NCT02168829) is a multicenter randomized controlled trial designed to examine the optimal method of stroke prevention for patients after successful AF ablation who are at risk for stroke based on their CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes mellitus, previous stroke/transient ischemic attack (TIA) (2 points), vascular disease, age 65–74 years, sex class (female)) score. Among patients without apparent atrial arrhythmia recurrences for at least 12 months after AF ablation, we hypothesize that the use of rivaroxaban will reduce the rate of stroke, systemic embolism, and covert embolic stroke (defined by cerebral magnetic resonance imaging (MRI)) when compared to acetylsalicylic acid (ASA).

Methods

Study design

The OCEAN trial is a multicenter, 2-arm randomized controlled trial with a prospective, randomized, blinded endpoint (PROBE) design. It is enrolling subjects at risk for stroke and who have not had clinically apparent atrial fibrillation, flutter, or tachycardia (AF/AFL/AT) recurrences for at least 12 months after their most recent paroxysmal, persistent, or longstanding

persistent AF ablation procedure. Eligible and consenting subjects will be randomized in a 1:1 ratio to OAC therapy (rivaroxaban 15 mg daily) or single antiplatelet therapy (ASA 75-160 mg daily). Randomization with concealed allocation will be performed using blocked cells of varying sizes using web-based software (Dacima, Montreal, Canada). Outcomes will be adjudicated by personnel who are blinded to subjects' randomization status. All sites will obtain approval from their respective ethics committees and the study procedures will be performed with the principles of Good Clinical Practice and the Declaration of Helsinki. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents

Study setting and timeline

This is a multicenter trial involving AF ablation centers in Canada, Germany, the United Kingdom, Belgium, Australia, and China. As of Dec 3, 2017, 14 Canadian centers and 1 Chinese site have been activated and 219 subjects are enrolled. We aim to complete enrollment in 24 months and subjects will be followed for 36 months.

Funding

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Study Population

Written informed consent will be obtained from each subject. For a subject to be eligible for study enrollment, at least 12 months must have elapsed after his/her last catheter ablation for AF without evidence of clinically apparent atrial arrhythmia recurrence. Having no "clinically apparent atrial arrhythmia recurrence" is defined by the absence of ≥ 30 seconds of AF/AFL/AT in: (i) at least one 24-hour Holter and ECG within the first 2-6 months after the last ablation procedure, and (ii) at least one 24-hour Holter and ECG beyond 6 months after the last ablation. If the last Holter and ECG were not performed within 2 months prior to study enrollment, subjects must undergo an ECG and a Holter (preferably 48-hour) demonstrating absence of ≥ 30 seconds of AF/AFL/AT (Figure 1). Given that prolonged rhythm monitoring is not available for all subjects after AF ablation, this screening approach provides a pragmatic definition of "no arrhythmia recurrence" in our study. Subjects who remain treated with anti-arrhythmic drugs for ≥ 12 months after their most recent ablation procedure are eligible for study enrollment. However, we anticipate that most, if not all, subjects in this trial will not be treated with anti-arrhythmic drugs at the time of study enrollment. This trial will enroll subjects with CHA₂DS₂-VASC scores of ≥ 1 . Subjects with a CHA₂DS₂-VASC score of 1 on the basis of female sex or vascular disease alone are required to have at least one additional risk factor to be eligible for inclusion. This entry criterion is chosen to enrich a patient cohort who otherwise is at lower risk for stroke relative to the general AF population.^{9,20} Subjects with ischemic or non-ischemic cardiomyopathy are eligible for study enrollment unless they have prosthetic valves, mitral valve repair, or rheumatic mitral stenosis. Furthermore, our study eligibility criteria does not include a cut-off for left atrial size. The full inclusion and exclusion criteria are listed in Table 1.

Interventions

Subjects will be randomized in a 1:1 ratio to OAC or single antiplatelet therapy. The study flow chart is outlined in Figure 2.

NOAC therapy

In the intervention arm, subjects are treated with rivaroxaban 15 mg daily. The rationale for choosing a rivaroxaban dose of 15 mg was supported by pharmacokinetic and clinical trial data which suggested that this dose could be safely used in the AF population without a discernible signal of increased harm or decreased efficacy.²¹⁻²³ Additional details on the rationale for the choice of this rivaroxaban dose are discussed in the Supplementary Appendix. No dose adjustment will be performed for patients with creatinine clearance of 30-49 ml/min, although it is expected that the number of patients with creatinine clearance of <50 ml/min will not be substantial in a post-ablation population. If the subject cannot tolerate rivaroxaban due to side effects, another NOAC agent may be prescribed. If dabigatran is prescribed, the dose will be 110 mg twice daily. Given the absence of evidence to support the use of apixaban and edoxaban at reduced doses for subjects with preserved renal function, standard doses of these drugs will be prescribed if they are used in this trial.

Single antiplatelet therapy

Subjects randomized to the control arm are treated with ASA at 75-160 mg daily. This range is provided to accommodate for differences in ASA dosing in various countries. It is expected that most patients will receive 81 mg daily. Since all of the patients in this trial will have one or more risk factors for stroke and a significant proportion will have other vascular

disease, we felt that the comparator arm should use antiplatelet therapy. No antiplatelet therapy is only suggested in guidelines for those patients with no risk factors for stroke.^{3, 24} If the subject is intolerant or allergic of ASA, no other antiplatelet agent will be substituted unless there is a clinical need to do so (e.g. PCI or ACS).

Management of the need for temporary oral anticoagulation and/or antiplatelet therapy in each of the randomization arms

It is anticipated that patients may undergo coronary intervention procedures electively or in the setting of an acute coronary syndrome which would require temporary adjustments in antiplatelet therapy. Furthermore, some patients will experience recurrences of AF for which cardioversion may have to be performed with more intensive oral anticoagulation. In both of these cases, the protocol outlines specific measures for management to minimize crossovers and disparity in patient treatment. These are outlined in the Supplementary Appendix.

If a patient undergoes repeat catheter ablation for AF, the patient will be censored at that point in time and exited from the study. Subjects who undergo ablation for arrhythmias other than AF (such as supraventricular tachycardia, right atrial flutter, ventricular arrhythmia, left atrial flutter/tachycardia not involving the pulmonary veins) will not be exited from the trial.

Assessments:

Brain MRI

All subjects will undergo brain MRI scans at 3 time points: (i) prior to randomization, (ii) 12 months, and (iii) 36 months to detect covert strokes. Brain MRI scanning will be performed according to study specified protocols including diffusion-weighted MRI (DW-MRI) and T2

weighed fluid attenuated recovery (FLAIR) imaging (Supplementary Appendix). These scans will be read by core lab personnel blinded to treatment allocation (University of Calgary, Calgary, Alberta, Canada). The MRI results will not be routinely disclosed to the investigators or subjects. In the case of urgent unexpected MRI findings (like a brain tumor), neuro-radiology experts at the core laboratory will make recommendations to the coordinating center which will then inform the appropriate site.

Implantable loop recorder

In a pre-specified sub-study, 500 subjects will undergo insertion of an implantable loop recorder (ILR) with automated AF detection software (BioMonitor 2.0®, Biotronik, Germany). This technology provides continuous arrhythmia monitoring and allows us to examine the relationship between AF recurrence and burden to subjects' long-term risk of clinical or covert stroke after ablation. Insertion and programming of the ILRs will be performed using standardized guidelines. All ILR data will be collected by remote monitoring and collected in a core lab (University of Ottawa, Ottawa, Canada) for independent adjudication by cardiologists who are blinded to treatment allocation. Results of the ILR will not be disclosed to investigators or subjects except for the occurrence of serious, non-AF arrhythmias (e.g. sustained ventricular tachycardia).

Primary outcome

The primary outcome is a composite of all clinically overt stroke²⁵, systemic embolism²⁵, and incident covert stroke as detected by cerebral MRI. It is assumed that the direction of treatment effect for each of the components of the primary outcome will be the same. Stroke is

defined as a sudden, focal neurologic deficit resulting from a presumed cerebrovascular cause that is not reversible within 24 hours and not due to a readily identifiable cause, such as a tumor or seizure.²⁵ Brain imaging is sought in each case to help distinguish hemorrhagic from ischemic stroke. Subjects dying from any cause within 30 days of the onset of stroke are regarded as having fatal stroke.²⁵ Non-central nervous system systemic embolism is defined as abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (eg, trauma, atherosclerosis, or instrumentation).²⁵ In the presence of atherosclerotic peripheral arterial disease, the diagnosis of embolism to the lower extremities requires angiographic demonstration of abrupt arterial occlusion.²⁵ Covert stroke is defined as the presence of one or more lesions >15 mm^{26,27} detected between the baseline, and one or more of the one year, and final (three year) MRI on T2 weighted and/or FLAIR MRI scanning protocols. Rationale for the 15 mm cutoff is provided in the Supplementary Appendix.

Secondary outcomes

Each component of the primary outcome will be assessed as a secondary outcome. In addition, we will assess the incidence of major bleeding, clinically relevant non-major bleeding, minor bleeding, and their composite as defined by the International Society of Thrombosis and Haemostasis (ISTH).^{28,29} Other secondary outcomes include: clinically-overt intracranial hemorrhage (ICH); microbleeds as detected by MRI³⁰; transient ischemic attack (TIA) defined as presence of a new focal neurologic deficit thought to be vascular in origin with signs or symptoms lasting <24 hours without evidence of infarction (assessed with brain imaging)³¹; all-cause mortality; net clinical benefit based on reduction in stroke/TIA rate compared to major bleeding events; occurrence of non-primary endpoint MRI changes from baseline to final scan

such as: total number of new MRI lesions with sizes of >3 mm, >5 mm, >15 mm, and >20 mm; correlation of AF burden/recurrence to occurrence of clinical or covert stroke; neuropsychological testing (Montreal cognitive assessment (MoCA) and the Modified mini mental state exam (3MSE)) at baseline and at 3-year follow-up; quality of life with the EQ-5D-5L questionnaire and the visual analog scale at baseline, 1-year, and 3-year follow-up; and cost utilization/effectiveness analysis.

Outcome adjudication

Outcomes will be adjudicated by a clinical events committee, consisting of cardiologists and neurologists who are blinded to subjects' treatment assignment.

Planned analyses

Descriptive statistics including 95% confidence intervals will be calculated for baseline variables using means, medians, standard deviations and interquartile ranges for continuous outcomes, and rates and proportions for discrete outcomes for each treatment arm.

The primary analysis will be conducted with the intention-to-treat principle. For the primary outcome, the OAC versus ASA arms will be compared using the chi-square test. Time-to-event analysis for the primary outcome will not be performed since the exact timing of covert stroke cannot be determined based on the baseline, 12-month, and 36-month MRI scans alone. A secondary, on-treatment analysis will be conducted to account for subjects who crossed over or discontinued their assigned therapy during the study. A subject will be classified as crossover if he/she permanently changes to the other treatment arm for any reason other than those

specifically defined in the protocol as a short-term change in treatment (e.g. those who underwent PCI or cardioversion). A permanent change is defined as >3 months.

An interim analysis for efficacy is planned after all subjects have completed their 1-year MRI scans. This would occur at approximately year 3 of the study. We assume that all of the patients are recruited into the study in a stepped uniform fashion, with increasing enrollment as more centers are activated in the study, and that study events occur in a uniform fashion over the 3 year follow-up period. It is estimated that approximately 55% of the expected events in the study will have occurred at the time of interim analysis, but the actual level of information will be determined at that time. Considering a flexible monitor perspective for the planned group sequential method, and using the Lan and DeMets error spending approach, with O'Brien-Fleming type boundaries, the alpha values for the interim and final analyses will be determined preserving the overall two-sided type I error rate of 0.05. An independent Data Safety and Monitoring Board (DSMB) is in place which will evaluate the results and provide recommendations on trial continuation and sample size.

Data collection and management

After the baseline and randomization visit, subjects will be seen at in-person follow-up visits at 6 and 12 months and then annually. An exit visit will occur at study end. The following information will be collected at each visit: medical history; stroke; systemic embolism; bleeding events; medications; and 12-lead electrocardiograms. It is recommended that all patients undergo annual 48-hour Holter monitoring as standard of care. Quality of life assessment will occur at baseline, 12 months, and 36 months. Neuropsychological testing will be performed at baseline and 36 months.

The University of Ottawa Heart Institute (UOHI) Cardiovascular Methods Center is the coordinating center for all aspects of the OCEAN trial. Specifically, it will be responsible for the randomization process and for receiving, editing, processing, analyzing, and storing data generated in this trial. Data entry will be electronic and web-based. All endpoint outcomes will be assessed by blinded, independent adjudicators. Study safety oversight will be provided by an independent DSMB.

Sample size calculation

An annual primary outcome rate of 3.5% per year (consisting of an annual stroke rate of 1.6%³² and a covert stroke rate of 1.9% per year in the control group³³) is assumed. This trial is designed as a superiority trial to demonstrate that rivaroxaban 15 mg daily will result in a 1.4% absolute risk reduction (40% relative risk reduction) of the primary endpoint when compared to ASA. This magnitude of difference was estimated from the MRI sub-study of the Apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) trial which compared subjects treated with apixaban to those treated with ASA alone.³⁴ In the subset of patients with CHADS₂ score of 0-1, the relative risk reduction was 44%. In the OCEAN trial, the planned accrual rate is 2 years with a follow-up period of 3 years.

We anticipate a 5.75% dropout (e.g. due to repeat ablation) and crossover rates of 1.5% and 3.75% for the rivaroxaban and ASA arms, respectively. Based on these assumptions, with a two-sided alpha of 0.05 and a power of 80%, a total sample size of 1572 patients will be required (786 in each arm).

Discussion

The optimal long-term OAC management for patients after successful AF ablation is currently unknown. In a Canadian survey, over 95% of electrophysiologists would discontinue OAC after successful ablation if their patients' CHADS₂ score was 1 or less.³⁵ In an European survey of electrophysiologists, 16% of them were comfortable with OAC cessation after successful ablation even if the patients' stroke risk were high (CHADS₂≥2).³⁶ Coupled with an acknowledged lack of evidence underpinning current guideline recommendations on this topic²⁻⁵, we believe that equipoise exists and hence justifies conduct of a randomized trial to address this question.

In addition to the more traditional clinical endpoints of stroke and systemic embolism, the OCEAN trial will assess if the incidence of covert stroke (as detected by brain MRI) differs between subjects treated with rivaroxaban versus ASA after apparently successful AF ablation. Covert stroke is defined as “imaging or neuropathological evidence of brain infarction, without a history of acute neurological dysfunction attributable to the lesion”.³⁷ Covert stroke may occur in 50-90% of patients with AF, even among those felt to be at low risk for stroke.³⁸⁻⁴⁰ In addition, covert stroke is estimated to be 2-7 times more common than the incidence of clinically manifest stroke in patients with AF.^{33,38,41,42} Although these infarctions are not immediately symptomatic, long-term studies suggest that such changes are related to future clinical stroke⁴³⁻⁴⁵, cognitive decline^{46,47}, dementia⁴⁸⁻⁵⁰, and increased mortality.^{51,52} Thus, AF-related covert stroke as detected by MRI is an area of emerging importance.⁵³ The OCEAN trial will afford us an opportunity to examine the association between AF and covert stroke and whether rivaroxaban use may alter its incidence when compared to ASA.

Despite the strong association between AF and stroke, the mechanism by which AF causes stroke is undefined and is a topic of considerable interest. Classically, it is believed that AF leads to clot formation due to stasis of blood in the left atrium, which in turn causes stroke. However, studies of patients with dual chamber pacemakers had demonstrated a temporal dissociation between the onset of AF and the occurrence of stroke in a sizeable proportion of them, raising the possibility that AF may be a marker of higher stroke risk rather than being a primary causal driver for stroke.^{54,55} In this respect, the ILR sub-study of OCEAN will provide additional insight on the causal relationship between AF and stroke. It may also inform us on the true risk of stroke associated with infrequent atrial high rate episodes in the post-ablation population.⁵⁶

In conclusion, the OCEAN trial is a multicenter, randomized controlled trial which examines if OAC will lower the risk of stroke, systemic embolism, and covert stroke amongst patients who have had successful AF ablation when compared to ASA. The results of this trial will help inform clinicians on the optimal antithrombotic regimen for post-ablation patients with risk factors for stroke.

Disclosures

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References

1. Piccini JP, Lopes RD, Kong MH, et al. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. *Circ Arrhythm Electrophysiol* 2009;2(6):626-33.
2. Verma A, Macle L, Cox J, et al. CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: catheter ablation for atrial fibrillation/atrial flutter. *Can J Cardiol* 2011;27(1):60-6.
3. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC Endorsed by the European Stroke Organisation (ESO). *Eur Heart J* 2016;37(38):2893-2962.
4. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. 2017 Oct;14(10):e275-444.
5. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;130(23):e199-267.
6. Kumar S, Walters TE, Halloran K, et al. Ten-year trends in the use of catheter ablation for treatment of atrial fibrillation vs. the use of coronary intervention for the treatment of ischaemic heart disease in Australia. *Europace* 2013;15(12):1702-9.

7. Deshmukh A, Patel NJ, Pant S, et al. In-hospital complications associated with catheter ablation of atrial fibrillation in the united states between 2000 and 2010: Analysis of 93 801 procedures. *Circulation* 2013;128(19):2104-12.
8. Kirchhof P, Breithardt G, Camm AJ, et al. Improving outcomes in patients with atrial fibrillation: rationale and design of the Early treatment of Atrial fibrillation for Stroke prevention Trial. *Am Heart J*. 2013;166(3):442-8.
9. Oral H, Chugh A, Ozaydin M, et al. Risk of thromboembolic events after percutaneous left atrial radiofrequency ablation of atrial fibrillation. *Circulation* 2006;114(8):759-65.
10. Rossillo A, Bonso A, Themistoclakis S, et al. Role of anticoagulation therapy after pulmonary vein antrum isolation for atrial fibrillation treatment. *J Cardiovasc Med (Hagerstown)* 2008;9(1):51-5.
11. Bunch TJ, Crandall BG, Weiss JP, et al. Warfarin is not needed in low-risk patients following atrial fibrillation ablation procedures. *J Cardiovasc Electrophysiol* 2009;20(9):988-93.
12. Themistoclakis S, Corrado A, Marchlinski FE, et al. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. *J Am Coll Cardiol* 2010;55(8):735-43.
13. Saad EB, d'Avila A, Costa IP, et al. Very low risk of thromboembolic events in patients undergoing successful catheter ablation of atrial fibrillation with a CHADS₂ score ≤ 3 : a long-term outcome study. *Circ Arrhythm Electrophysiol* 2011;4(5):615-21.
14. Yagishita A, Takahashi Y, Takahashi A, et al. Incidence of late thromboembolic events after catheter ablation of atrial fibrillation. *Circ J* 2011;75(10):2343-49.

15. Guiot A, Jongnarangsin K, Chugh A, et al. Anticoagulant therapy and risk of cerebrovascular events after catheter ablation of atrial fibrillation in the elderly. *J Cardiovasc Electrophysiol* 2012;23(1):36-43.
16. Winkle RA, Mead RH, Engel G, et al. Discontinuing anticoagulation following successful atrial fibrillation ablation in patients with prior strokes. *J Interv Card Electrophysiol* 2013;38(3):147-53.
17. Gaita F, Sardi D, Battaglia A, et al. Incidence of cerebral thromboembolic events during long-term follow-up in patients treated with transcatheter ablation for atrial fibrillation. *Europace* 2014;16(7):980-86.
18. Ha AC, Hindricks G, Birnie DH, et al. Long-term oral anticoagulation for patients after successful catheter ablation of atrial fibrillation: is it necessary? *Curr Opin Cardiol* 2015;30(1):1-7.
19. Raviele A, Natale A, Calkins H, et al. Venice Chart. VeniceChart international consensus document on atrial fibrillation ablation: 2011 update. *J Cardiovasc Electrophysiol* 2012;23(8):890-923.
20. Holmqvist F, Simon D, Steinberg BA, et al. Fibrillation (ORBIT-AF). Catheter ablation of atrial fibrillation in U.S. community practice -- results From Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *J Am Heart Assoc*. 2015;4(5):pii:e001901.
21. Mueck W, Stampfus J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. *Clin Pharmacokinet*. 2014;53(1):1-16.
22. Stampfuss J, Kubitza D, BeckaM, Mueck W. The effect of food on the absorption and pharmacokinetics of rivaroxaban. *Int J Clin Pharmacol Ther* 2013; 51(7):549-561.

23. Hori M, Matsumoto M, Tanahashi N, et al. J-ROCKET AF study investigators. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation – the J-ROCKET AF study. *Circ J*. 2012;76(9):2104-11.
24. Macle L, Cairns J, Leblanc K, et al. 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol* 2016;32(10):1170-85.
25. ROCKET AF study investigators. Rivaroxaban-Once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: Rationale and design of the ROCKET AF study. *Am Heart J* 2010;159(3):340-347.
26. Potter GM, Marlborough FJ, Wardlaw JM. Wide variation in definition, detection, and description of lacunar lesions on imaging. *Stroke* 2011;42(2):359-66.
27. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet neurology* 2013;12(8):822-38.
28. Schulman S, Angerås U, Bergqvist D, et al. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010;8(1):202-4.
29. Kaatz S, Ahmad D, Spyropoulos AC, et al. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic

disease in non-surgical patients: Communication from the SSC of the ISTH. *J Thromb Haemost.* 2015;13(11):2119-2126.

30. Kirchhof P, Breithardt G, Aliot E et al. Personalized management of atrial fibrillation: Proceedings from the fourth Atrial Fibrillation competence NETwork/European Heart Rhythm Association consensus conference. *Europace.* 2013;15(11):1540-56.
31. Easton JD, Saver JL, Albers GW et al. Definition and evaluation of transient ischemic attack. *Stroke.* 2009;40(6):2276-93.
32. Reynolds MR, Gunnarsson CL, Hunter TD, et al. Health outcomes with catheter ablation or antiarrhythmic drug therapy in atrial fibrillation: Results of a propensity-matched analysis. *Circulation Cardiovasc Qual Outcomes* 2012;5(2):171-81.
33. Ezekowitz MD, James KE, Nazarian SM, et al. Silent cerebral infarction in patients with nonrheumatic atrial fibrillation. The veterans affairs stroke prevention in nonrheumatic atrial fibrillation investigators. *Circulation* 1995;92(8):2178-82.
34. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *The New England journal of medicine.* 2011;364:806-817.
35. Mardigyan V, Verma A, Birnie D, et al. Anticoagulation management pre- and post-atrial fibrillation ablation: A survey of Canadian centres. *Can J Cardiol* 2013;29(2):219-23.
36. Lip GY, Proclemer A, Dagres N, et al. Periprocedural anticoagulation therapy for devices and atrial fibrillation ablation. *Europace* 2012;14(5):741-44.
37. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44(7):2064-89.

38. Feinberg WM, Seeger JF, Carmody RF, et al. Epidemiologic features of asymptomatic cerebral infarction in patients with nonvalvular atrial fibrillation. *Arch Intern Med* 1990;150(11):2340-44.
39. Gaita F, Corsinovi L, Anselmino M, et al. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. *J Am Coll Cardiol* 2013;62(21):1990-97.
40. De Leeuw FE, de Groot JC, Oudkerk M, et al. Atrial fibrillation and the risk of cerebral white matter lesions. *Neurology* 2000;54(9):1795-1801.
41. Bernhardt P, Schmidt H, Hammerstingl C, et al. Patients with atrial fibrillation and dense spontaneous echo contrast at high risk a prospective and serial follow-up over 12 months with transesophageal echocardiography and cerebral magnetic resonance imaging. *J Am Coll Cardiol* 2005;45(11):1807-12.
42. Bernhardt P, Schmidt H, Hammerstingl C, et al. Patients at high risk with atrial fibrillation: A prospective and serial follow-up during 12 months with transesophageal echocardiography and cerebral magnetic resonance imaging. *J Am Soc Echocardiogr* 2005;18(9):919-24.
43. Gouw AA, van der Flier WM, Fazekas F, et al. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: The leukoaraiosis and disability study. *Stroke* 2008;39(5):1414-20.
44. Melkas S, Sibolt G, Oksala NK, et al. Extensive white matter changes predict stroke recurrence up to 5 years after a first-ever ischemic stroke. *Cerebrovasc Dis* 2012;34(3):191-8.

45. Oksala NK, Oksala A, Pohjasvaara T, et al. Age related white matter changes predict stroke death in long term follow-up. *J Neurol Neurosurg Psychiatry* 2009;80(11):762-6.
46. De Groot JC, De Leeuw FE, Oudkerk M, et al. Periventricular cerebral white matter lesions predict rate of cognitive decline. *Ann Neurol* 2002;52(3):335-41.
47. Farina E, Magni E, Ambrosini F, et al. Neuropsychological deficits in asymptomatic atrial fibrillation. *Acta Neurol Scand* 1997;96(5):310-16.
48. Inzitari D, Pracucci G, Poggesi A, et al. Changes in white matter as determinant of global functional decline in older independent outpatients: Three year follow-up of LADIS (leukoaraiosis and disability) study cohort. *BMJ* 2009;339:b2477.
49. Knecht S, Oelschlager C, Duning T, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *Eur Heart J* 2008;29(17):2125-32.
50. Rastas S, Verkkoniemi A, Polvikoski T, et al. Atrial fibrillation, stroke, and cognition: A longitudinal population-based study of people aged 85 and older. *Stroke* 2007;38(5):1454-60.
51. Bokura H, Kobayashi S, Yamaguchi S, et al. Silent brain infarction and subcortical white matter lesions increase the risk of stroke and mortality: A prospective cohort study. *J Stroke Cerebrovasc Dis* 2006;15(2):57-63.
52. Conijn MM, Kloppenborg RP, Algra A, et al. Cerebral small vessel disease and risk of death, ischemic stroke, and cardiac complications in patients with atherosclerotic disease: The second manifestations of arterial disease-magnetic resonance (SMART-MR) study. *Stroke* 2011;42(11):3105-09.

53. Koton S, Tsabari R, Molshazki N, et al. Burden and outcome of prevalent ischemic brain disease in a national acute stroke registry. *Stroke* 2013;44(12):3293-97.
54. Glotzer TV, Hellkamp AS, Zimmerman J, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MODe Selection Trial (MOST). *Circulation*. 2003;107(12):1614-9.
55. Brambatti M, Connolly SJ, Gold MR, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation*. 2014;129(21):2094-9.
56. Camm AJ, Simantirakis E, Goette A et al. Atrial high-rate episodes and stroke prevention. *Europace* 2017;19(2):169-179.

Table 1. Study Inclusion and Exclusion CriteriaInclusion Criteria

1. Patient must be at least one year post-successful catheter ablation(s) for atrial fibrillation without evidence of any clinically apparent arrhythmia recurrence defined as all of the following: No AF/AT/AFL on at least 24 hour Holter and an ECG (or equivalent) from 2-6 months after the last ablation, AND no AF/AT/AFL on at least 24 hour Holter and an ECG any time after 6 months after the last ablation AND no AF/AT/AFL on at least 24 hour Holter and ECG 2 months before enrolment in the study. The Holter/ECG within 2 months of enrolment may also serve as the Holter/ECG performed 6 months or later after the last ablation – see section 2.3.1.
2. Patient must have a CHA₂DS₂-VASc risk score of 1 or more. Patients in whom female sex or vascular disease are their **sole** risk factor may not be enrolled.
3. Patient must be >18 years of age.
4. Patient must have non-valvular AF (such as valvular prosthesis, rheumatic mitral stenosis, mitral valve repair)

Exclusion Criteria

1. Patient does not meet all of the above listed inclusion criteria.
2. Patient is unable or unwilling to provide informed consent.
3. Patient is included in another randomized clinical trial or a clinical trial requiring an insurance.
4. Patient has been on an investigational drug within 30 days of enrolment.

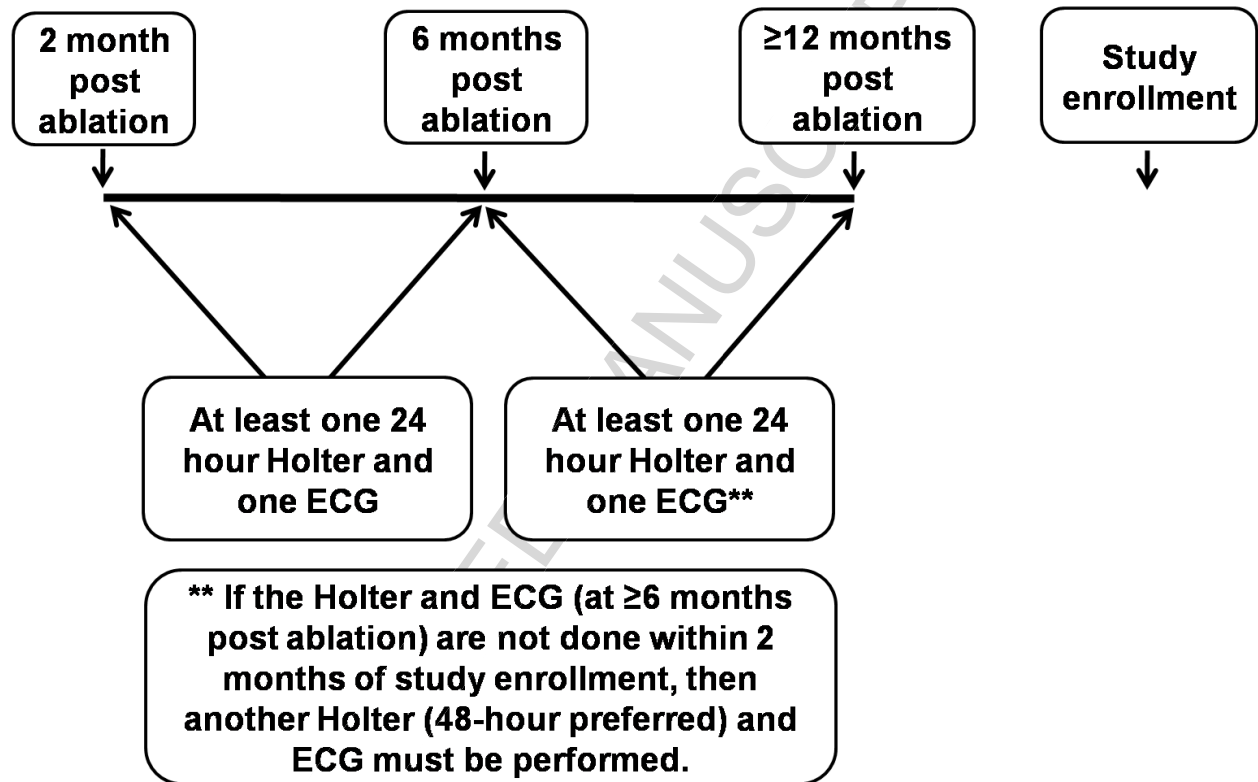
5. Patient has been on strong CYP3A inducers (such as rifampicin, phenytoin, phenobarbital, or carbamazepine) or strong CYP3A inhibitors (such as ketoconazole or protease inhibitors) within 4 days of enrolment.
6. Patient has creatinine clearance < 30 mL/min.
7. Patient has bleeding contra-indication to oral anticoagulation (such as bleeding diathesis, hemorrhagic disorder, significant gastrointestinal bleeding within 6 months, intracranial/intraocular/atraumatic bleeding history, fibrinolysis within 48 hours of enrollment).
8. Patient has other contraindication to oral anticoagulation or treatment with antiplatelet agent (such as allergy).
9. Patient has a contraindication to magnetic resonance imaging (MRI) or is unlikely to tolerate due to severe claustrophobia.
10. Patients with a contraindication to implantation of an implantable loop recorder (such as limited immunocompetence or a wound healing disorder).
11. Patient has valvular atrial fibrillation (valvular prosthesis, rheumatic mitral stenosis, mitral valve repair).
12. Patient has a non-arrhythmic condition necessitating long-term oral anticoagulation.
13. Patient had a severe, disabling stroke within one year prior to enrollment or any stroke within 14 days of enrollment.
14. Patient with special risk factors for stroke unrelated to AF, specifically known thrombophilia/hypercoagulability, uncontrolled hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg within 4 days of enrollment), untreated

familial hyperlipidemia, known vascular anomaly (intracranial aneurysm/arteriovenous malformation or chronic vascular dissection), or known severe carotid disease.

15. Pregnancy or breastfeeding.
16. Women of childbearing age who refuse to use a highly effective and medically acceptable form of contraception throughout the study.
17. Patients who are > 85 years of age.
18. Patients who are critically ill or who have a life expectancy <3 years.
19. Patients for whom the investigator believes that the trial is not in the interest of the patient.

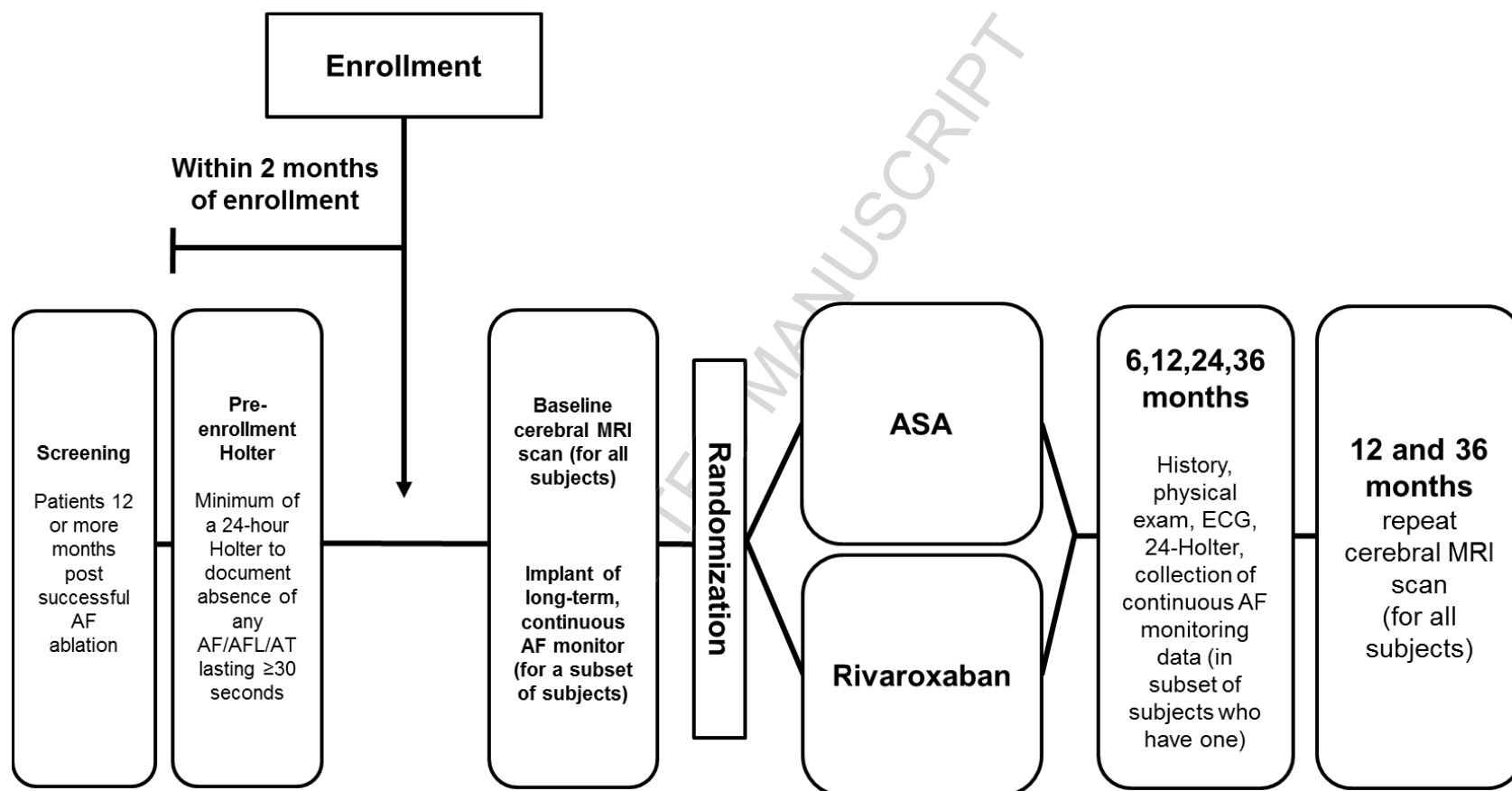
AF = Atrial Fibrillation; AFL = Atrial Flutter; AT = Atrial Tachycardia; ECG = Electrocardiogram; MRI = Magnetic Resonance Imaging.

Figure 1. Minimum screening criteria for atrial fibrillation, atrial flutter, or atrial tachycardia prior to inclusion into the OCEAN study.



The Holter and ECG performed within 2 months of enrolment may also serve as the Holter and ECG beyond 6 months post-ablation.

Figure 2. Study flow diagram for the OCEAN trial.



AF= Atrial Fibrillation; AFL = Atrial Flutter; ASA = Acetylsalicylic Acid; AT = Atrial Tachycardia; ECG = Electrocardiogram; MRI = Magnetic Resonance Imaging.